Assessment of Risk Factors for Ventilator Associated Pneumonia in the Medical Intensive Care Unit

İç Hastalıkları Yoğun Bakım Ünitesinde Ventilator İlişkili Pnömoni İçin Risk Faktörlerinin Değerlendirilmesi

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Abstract

Aim: To detect the risk factors for ventilator associated pneumonia (VAP) and role of ventilator parameters in the development of VAP in a Medical Intensive Care Unit (MICU).

Materials and Methods: This study was performed prospectively in Gevher Nesibe Hospital MICU of Erciyes University Medical Faculty between 1 January, 2003 and 1 April, 2004. The patients, who were 16 years old and over, who had been ventilated with a mechanical ventilator for more than 24 hours and who had no pulmonary infection, were included in the study. The patients' demographic characteristics, risk factors and ventilator parametres (PEEP, ventilation mode, tidal volume, FiO_2, PEAK, mean pressure, plateau pressure) were recorded. Also the hospitalization period before mechanical ventilation and up to pneumonia development, total time of ICU admission and the time of weaning were recorded.

Results: A total of 106 patients were included in the study and VAP developed in 49 (46.2%) patients. When risk factors for VAP were evaluated in the univariate analysis, it was found that there was a statistically significant relationship between previous sepsis (OR=2.557, 95% CI=1.153-5.671, p=0.021), sedative drug usage (OR=2.876, 95% CI=1.168-7.075, p=0.021), tracheostomy (OR=3.602, 95% CI=1.446-8.972, p=0.006), PIP (OR=0.946, 95% CI=0.898-0.997, p=0.036), number of aspirations (OR=1.778, 95% CI=1.238-2.552, p=0.002), enteral nutrition (OR=5.440, 95% CI=2.197-13.471, p=0.000) and nasogastric tube (OR=2.510, 95% CI=1.138-5.537, p=0.023). When multivariate analysis was performed, previous sepsis (OR=6.291, 95% CI=1.944-20.356, p=0.002), sedative drug usage (OR=3.719, 95% CI=1.109-12.476, p=0.033), number of aspiration (OR=2.107, 95% CI=1.313-3.381, p=0.002) and enteral nutrition (OR=3.586, 95% CI=1.063-12.100, p=0.040) were determined to be independent risk factors. Ventilation modes and ventilation parameters had no effect on the development of pneumonia with multivariate logistic regression analysis. The duration of hospitalization in patients with VAP was longer than those who had no VAP (p<0.05). The crude mortality rate was 81.6%. There was no statistically significant relationship in mortality rates between the patients with VAP and those without VAP (p>0.05).

Conclusion: Sepsis, sedative drug usage, number of aspirations and enteral nutrition were established as risk factors, whereas ventilation modes and ventilation parameters had no effect on the development of pneumonia. Avoiding unnecessary aspiration and sedation, rapid diagnosis and treatment of infections in other systems will be effective in the prevention of VAP. (Yoğun Bakım Derg 2011; 2: 34-8)

Key words: Ventilator-associated pneumonia, mechanical ventilation, ventilatory parameters and modes, risk factors

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Özet

Amaç: İç Hastalıklar Yoğun Bakım Ünite (İHYBÜ)'sinde ventilator ilişkili pnömoni (VİP) için risk faktörlerinin saptanması ve ventilator parametrelerinin VİP gelişimi üzerine etkisinin araştırılması amaçlandı.

Gereç ve Yöntemler: Bu çalışma 1 Ocak 2003-1 Nisan 2004 tarihleri arasında Erciyes Üniversitesi Tıp Fakültesi Gevher Nesibe Hastanesi İHYBÜ'sinde prospektif olarak yapıldı. İHYBÜ'sinde 16 yaş ve üzeri, 24 saatten fazla mekanik ventilatöre bağlı kalan ve yatışta akciğer enfeksiyonu olmayan hastalar çalışmaya alındı. Hastaların demografik özellikleri, VİP gelişimi için risk faktörleri ve ventilatör parametreleri (PEEP, ventilasyon modu, tidal volüm, FiO_2, PEAK, Mean pressure, plato basıncı) kaydedildi. Ayrıca ventilatöre bağlanmadan önce hastanede yatış süresi, pnömoni gelişinceye kadar hastanede yatış süresi, toplam yoğun bakımda yatış süresi ve ventilatörden ayrılma süreleri kaydedildi.

Bulgular: Toplam 106 hasta çalışmaya dahil edildi ve 49 (%46.2)'unda VİP gelişti. VİP gelişimi için risk faktörleri incelendiğinde, tek değişkenli analizde, önceden sepsis varlığı (OR=2.557 %95 CI=1.153-5.671 p=0.021), sedatif ilaç kullanımı (OR=2.876, %95 CI=1.168-7.075, p=0.021), trakeostomi açılması (0R=3.602, %95 CI=1.446-8.972, p=0.006), PIP (OR=0.946, %95 CI=0.898-0.997, p=0.036), aspirasyon sayısı (OR=1.778, %95 CI=1.238-2.552, p=0.002), enteral beslenme (OR=5.440, %95 CI=2.197-13.471, p=0.000) ve nazogastrik sonda takılması (OR=2.510, %95 CI=1.138-5.537, p=0.023) istatiksel olarak anlamlı bulundu. Çok değişkenli analizde ise önceden sepsis varlığı (OR=6.291, %95 CI=1.944-20.356, p=0.002), sedatif ilaç kullanımı (OR=3.719, %95 CI=1.109-12.476, p=0.033), aspirasyon sayısı (OR=2.107, %95 CI=1.313-3.381, p=0.002) ve enteral beslenme (OR=3.586, %95 CI=1.063-12.100, p=0.040) bağımsız risk faktörleri idi. Çok değişkenli analizde, ventilatör modlarının ve parametrelerinin VİP gelişimi üzerine etkisi izlenmedi. VİP gelişen hastalarda hastanede kalış süresi gelişmeyenlere göre daha fazla idi (p<0.05). Kaba mortalite oranı %81.6 idi. Ancak VİP gelişen ve gelişmeyen hastalar arasında mortalite açısından anlamlı fark yoktu (p>0.05).

Sonuç: Sepsis, sedatif ilaç kullanımı, aspirasyon sayısı ve enteral beslenme VİP gelişimi için risk faktörü iken, ventilatör modlarının ve parametrelerinin VİP gelişimi üzerine etkisi izlenmedi. Gereksiz aspirasyon ve sedasyondan kaçınılması, başka bölgedeki enfeksiyonların hızlı tespiti ve tedavisi VİP gelişiminin önlenmesinde katkı sağlayacaktır. (Yoğun Bakım Derg 2011; 2: 34-8)

Anahtar sözcükler: Ventilatör ilişkili pnömoni, mekanik ventilator, ventilatör parametreleri ve modları, risk faktörleri

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Introduction

Ventilator associated pneumonia (VAP) is the leading cause of morbidity and mortality in intensive care units (ICU). The reported incidence is 9-27% among all intubated patients and the crude mortality rates have ranged from 20-70% with 50% attributable mortality. Furthermore, VAP is associated with increased hospital stay with an additional 4-13 days and $40 000 excess cost per patient (1). However, infection control measures are more cost-effective and save $13 340 for every episode of VAP (2). Despite the preventive measures against defined risk factors, VAP continues to be a major problem for critically ill patients. The aim of this study was to identify "new" risk factors for VAP in order to guide the implementation of preventive measures, and focus on the effect of the ventilator parameters on the development of VAP.

Methods

The study was carried out between January 2003 and April 2004 prospectively in a medical intensive care unit (MICU) with nine beds. All patients were covered by an intensive care specialist for 24 hours, seven days a week and consulted with an infectious disease specialist on daily basis. Patients were included into the study if they were >16 years old and mechanically ventilated for more than 48 hours. Pregnancy, admission secondary to aspiration, and pneumonia at the time of inclusion was exclusion criteria.

Data collection included age, gender, underlying diseases, APACHE II and SOFA scores on admission, prior hospital admission and operation, length of stay in ICU before initiation of mechanical ventilation, presence of infection at another site, indication for mechanical ventilation, clinical outcome, length of ICU and hospital stay, prior antimicrobial therapy, sedation and previous sepsis (3). Furthermore, ventilator parameters (ventilation modes, positive end-expiratory pressure (PEEP), tidal volume (V_T), peak inspiratory pressure (PIP), FiO_2, mean airway pressure (Paw), plateau pressure (Ppl), respiratory rate), reintubation before the development of VAP, presence of nasogastric tube, enteral nutrition and tracheostomy, frequency of suctioning before the development of VAP (during the study period open-suction system was used) were recorded.

Ventilator associated pneumonia was considered when new and persistent pulmonary infiltrates, not otherwise explained, appeared on chest radiographs. Moreover, at least two of the following criteria were also required: 1) fever ≥38°C or ≤35.5°C, 2) leukocytosis ≥10 000/mm^3, 3) purulent respiratory secretions, 4) isolation of ≥10^5 bacteria from quantitative cultures of endotracheal secretions (4).

Microbiology

Giemsa stains of endotracheal secretions were performed for all patients. Samples containing more than 25 polymorphonuclear leucocytes and fewer than 10 (x100) epithelial cells were classified as purulent. Quantitative cultures of all purulent samples were performed using standard methods. Susceptibility testing was performed by disc diffusion method.

Statistical Analysis

Demographic characteristics of patients, prior hospital admission and operation, length of stay in ICU before initiation of mechanical ventilation, presence of infection at another site, indication for mechanical ventilation, clinical outcome, length of ICU and hospital stay, prior antimicrobial therapy, sedation, previous sepsis and ventilator parameters were compared using univariate and multivariate logistic regression and chi-square tests. Independent-sample T test was used to compare the extra length of stay. Data were given as mean±SD and a p-value of <0.05 was accepted as significant.

Results

During the study period, 919 patients were admitted to the ICUs and 168 (18.3%) were mechanically ventilated. Among these patients, 62 had pneumonia on admission and were excluded from the study. Overall, 106 patients were evaluated for the development of VAP. The mean±SD age of these patients was 56.9±19.7 years (range, 16 to 91). Fifty-eight (54.7%) patients were male and 48 (45.3%) were female. The mean±SD APACHE II score was 19.8±6.1 (range, 6-38) and SOFA score was 8.5±2.9 (range, 3-16) on admission. At least one underlying disease was present in 85 (80.2%) patients.

Patients were mechanically ventilated for respiratory failure (n=94, 88.7%), postoperative respiratory insufficiency (n=8, 7.5%) and cardiopulmonary arrest (n=4, 3.8%). Sixty-four (60.4%) patients were ventilated with volume control mode and 42 (39.6%) patients were ventilated with pressure control ventilation. The ventilator parameters are shown in Table 1. Twenty-five (23.6%) patients were extubated successfully, and the mean weaning time was 6.3±5.3 days (range, 1-19).

During the study period, 49 (46.2%) patients developed VAP and the device-related incidence rate was 57.2/1000 ventilation days. The demographic characteristics of patients with VAP and without VAP are shown in Table 2. The mean±SD length of stay in ICU before the ventilation was 3.5±6.0 days (range, 0-35 days) and the mean±SD days for the development of pneumonia was 7.6±5.2 days (range, 3-25) (Figure 1). The mean length of stay in ICU was 15.0±11.4 days (range, 4-56 days) and 5.8±4.3 days (range, 1-26 days) for the patients with VAP and without VAP, respectively (p<0.001).

Univariate analysis suggested the following risk factors for the development of VAP; previous sepsis (67.3% in patients with VAP, 43.9% in patients without VAP), sedation, tracheostomy, number of suctioning, enteral nutrition, nasogastric tube and PIP. However, multivariate logistic regression showed that previous sepsis, sedation, number of suctioning

Table 1. Ventilator modes and parameters of patients with and without VAP

	Patients with VAP (n=49)	Patients without VAP (n=57)
Volume controlled mode (n) (%)	29 (59)	35 (61)
Pressure controlled mode (n) (%)	20 (41)	22 (39)
PEEP (mean±SD) (range)	6.8±2 (3-12)	6.3±2 (4-18)
Tidal volume (mean±SD) (range)	419±60 (225-550)	423±67 (280-600)
PIP (mean±SD) (range)	21.1±6.8 (6-38)	24.4±8.8 (5-50)
Paw (mean±SD) (range)	11.4±3.1 (5-19)	11.0±4.2 (5-33)
Plateau pressure (mean±SD) (range)	14.1±6.5 (5-29)	16.2±6.7 (6-33)
Respiratory rate (mean±SD) (range)	21 ±6 (12-40)	19±7 (12-43)
FiO_2 (mean±SD) (range)	50±48 (20-80)	46±9 (35-85)

PIP: Peak inspiratory pressure, Paw: mean airway pressurer

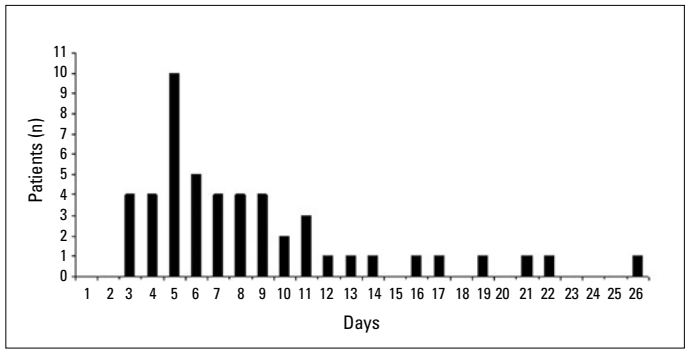

Figure 1. Days for the development of pneumonia

Table 2. Demographic characteristics of patients with and without VAP

	Patients with VAP (n=49)	Patients without VAP (n=57)
Age (mean±SD) (range)	55±20 (16-91)	58±18 (20-90)
Gender (male/female)	28/21	30/27
Underlying disease	n (%)	n (%)
Hypertension	12 (9.4)	15 (11.8)
Diabetes mellitus	9 (7.0)	14 (11.0)
Chronic obstructive lung disease	8 (6.2)	13 (10.2)
Chronic renal failure	8 (6.2)	6 (4.7)
Congestive cardiac failure	6 (4.7)	7 (5.5)
Cancer	6 (4.7)	4 (3.1)
Collagen vascular disease	3 (2.3)	3 (2.3)
Neurologic disorder	3 (2.3)	2 (1.5)

and enteral nutrition were significant independent risk factors for the development of VAP. On the other hand, infection at another site decreased the development of pneumonia (Table 3, 4). Neither ventilation modes nor mechanical ventilation parameters were risk factors for development of pneumonia with multivariate logistic regression (Table 5).

Microorganisms isolated from endotracheal aspirates are shown in Table 6. The resistance rates of most common pathogens were highly resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* (Figure 2) and *Staphylococcus aureus* (methicillin resistance rate was 100%).

Overall ICU crude mortality was 76.4% in ventilated patients. The difference between crude mortality rates for patients with VAP (82%) and without VAP (72%) was not significantly different (p>0.05).

Discussion

Mechanical ventilation is crucial for modern ICUs. However, VAP is the most common and fatal infection in mechanically ventilated patients. Also, it causes high morbidity and excess hospital cost with extra length of stay and requirement of antibiotics (1). More rational infection control measures and advances in our understanding of "new" risk factors for VAP will lead to the development of effective infection control measures. Many modifiable and non-modifiable risk factors have been established in previous studies. Age, pre-existing pulmonary disease, coma, head trauma, severity of underlying disease are some of the non-modifiable patient related risk factors and these are not goals of preventive measures. However, modifiable risk factors such as oropharyngeal colonization, aspiration, body position, sedation, use of H_2-antagonist, and enteral nutrition are obvious targets for infection control programs (4, 5). The primary goal of this study was to establish "new" modifiable risk factors for the development of "new" infection control measures.

Mechanical ventilation can damage the lungs and cause ventilator-associated lung injury (VALI). This injury promotes systemic inflamma-

Table 3. Results of univariate analysis of potential risk factors for VAP

Risk factors	OR	95% Confidence Interval	P
Age	0.993	0.974-1.013	0.500
Gender	0.865	0.400-1.873	0.714
APACHE-II	0.978	0.918-1.042	0.491
SOFA	0.948	0.829-1.083	0.430
Underlying disease	1.212	0.462-3.180	0.696
Prior hospital admission	0.556	0.256-1.205	0.138
Prior operation	0.417	0.135-1.282	0.127
Length of stay in ICU before ventilation	1.000	0.993-1.072	0.996
Reintubation before VAP	2.925	0.840-10.187	0.092
Prior antibiotic therapy	0.598	0.275-1.297	0.193
Infection at another site	0.402	0.174-0.929	0.033*
Previous sepsis	2.557	1.153-5.671	0.021*
Sedative drug usage	2.876	1.169-7.075	0.021*
Tracheostomy	3.602	1.446-8.972	0.006*
Number of aspiration	1.778	1.238-2.552	0.002*
Enteral nutrition	5.440	2.197-13.471	0.000*
Nasogastric tube	2.510	1.138-5.537	0.023*

* Statistically significant (p<0.05)

Table 4. Results of multivariate analysis of potential risk factors for VAP

Risk factors	OR	95% Confidence Interval	p
Tracheostomy	1.755	0.532-5.792	0.356
PIP	0.936	0.871-1.006	0.071
Nasogastric tube	1.332	0.444-3.993	0.609
Infection at another site	0.139	0.039-0.503	0.003*
Previous sepsis	6.291	1.944-20.356	0.002*
Sedative drug usage	3.719	1.109-12.446	0.033*
Number of aspiration	2.107	1.313-3.381	0.002*
Enteral nutrition	3.586	1.063-12.100	0.040*

* Statistically significant (p<0.05)

Table 5. Analysis of ventilation modes and parameters as a risk factor for VAP: results of univariate analysis

Risk factors	OR	95% Confidence Interval	p
Ventilation modes	1.149	0.524-2.522	0.728
PEEP	1.094	0.923-1.297	0.302
Tidal volume	0.999	0.993-1.005	0.730
FiO_2	1.004	0.991-1.018	0.545
PIP	0.946	0.898-0.997	0.036*
MawP	1.030	0.929-1.143	0.571
PP	0.951	0.880-1.028	0.204
Respiratory rate	1.034	0.997-1.094	0.248

*Statistically significant (p<0.05)

Table 6. Microorganisms isolated from endotracheal cultures

Microorganism	n (%)
Gram-negative	**54 (83.0)**
Acinetobacter baumannii	24 (44.4)
Pseudomonas aeruginosa	12 (22.2)
Eschericia coli	6 (11.1)
Klebsiella pneumoniae	4 (7.4)
Stenotrophomonas maltophilia	3 (5.5)
Proteus	2 (3.7)
Haemofilus influenza	1 (1.8)
Morexella catharralis	1 (1.8)
Aeromonas hyrofilia	1 (1.8)
Gram-positive	**11 (16.9)**
Staphylococcus aureus	10 (90.9)
Streptococcus pneumoniae	1 (9.1)

tion and causes the release of multiple mediators that increase the micropermeability of the alveolar sacs, allowing protein rich fluid, pulmonary edema, decreased compliance, cell necrosis and diffuse alveolar damage (6-8). In previous studies, an association between ventilator settings (high tidal volume, high plateau pressure, PEEP and respiratory rate) and VALI has been found (9-11). In this study, our hypothesis was

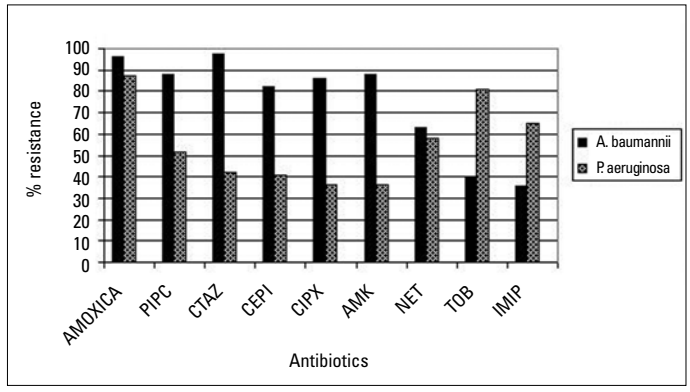

Figure 2. Resistance rates of *A. baumannii* and *P. aeruginosa*

that if ventilator parameters are a risk factor for VALI, they might be a risk factor for VAP because infection can arise easily in the injured lung. To our knowledge, there is no study that investigated the relationship between ventilator parameters and VAP. In this study, we investigated the effect of ventilator parameters (tidal volume, PEEP, PIP, plateau pressure, mean pressure, respiratory rate, FiO_2) on the development of VAP and they were not found to be risk factors for VAP.

On the other hand, 64 (60.4%) patients were ventilated in volume control ventilation and 42 (39.6%) patients were ventilated in pressure control ventilation. In this study, we hypothesized that these differences in ventilator modes may affect the development of pneumonia. However, there is no statistical difference between the effect of the two ventilation modes on the development of VAP.

The duration of MV increases the risk of infection. Cook et al. (12) reported a cumulatively increased risk of VAP with time, with 3% per day in the first week of MV, 2% per day in the second week, and 1% per day in the third week. In other studies, similarly, it was shown that the risk of pneumonia increased with the duration of MV and the highest risk was during the first 8-10 days (13-15). Also, in our study VAP mostly occurred between 3rd-11th days. The need for reintubation caused massive aspiration and associated with high incidence of VAP (16, 17). However, in our study reintubation was not found to be a risk factor.

The presence of a naso-gastric tube, enteral feeding and tracheostomy were described as risk factors for VAP in the literature (18). In our study, naso-gastric tube, enteral feeding and tracheostomy were found to be risk factors in univariate analysis, however in multivariate analysis only enteral feeding was an independent risk factor. Accurate evaluation of nutritional status and early initiation of enteral feeding is important, but the risk of gastric distention, colonization and aspiration increase the risk of VAP. Consequently, avoidance of unnecessary enterfal nutrition is crucial for the prevention of VAP. Also over-use of sedatives increase the duration of mechanical ventilation and risk of aspiration of oropharyngeal contents (19) and in our study sedation had a 3.7 fold increased risk for the development of VAP.

Prior hospital admission, operation and length of stay in ICU before the ventilation may increase the development of VAP by leading colonization of the aerodigestive tract (20). However in our study, they were not found to be a risk factor.

The role of systemic antibiotics in the development of VAP is controversial and is related to both an increased and a decreased risk for VAP. Sirvent et al. (21) reported that a short course of cephalosporin prophylaxis was associated with a lower rate of VAP in patients with structural coma. Also other investigators showed that antibiotics administered during the first days reduced the risk of early-onset ventilator associated pneumonia (22, 23). However, in the other studies,

prolonged antibiotic administration was identified as an independent risk factor (24, 25). In our study, previous use of antibiotics decreased the development of VAP, whereas it was not statistically significant. Moreover, infection at another site decreased the risk of VAP in univariate analysis. This may be explained by the prior use of antibiotics (30%) in these patients. On the other hand, previous sepsis in ICU was found as an independent risk for VAP. Diffuse alveolar epithelial injury occurring in sepsis may predispose VAP development in these patients.

Mortality rates were very high (76%) in our patients, as reported in our previous study (5). Highly resistant pathogens in our ICU may cause this high mortality rates, but several studies have showed that high mortality rates were a result of severe underlying illness and the patients do not die as a result of VAP, they die with VAP (26). Also, in our study, mortality rates between the patients with and without VAP were not statistically different. However, the length of stay in ICU was significantly high in patients with VAP as demonstrated in previous studies (27).

The primary goal of this study was to establish "new modifiable risk factors" for VAP and investigate the role of ventilator settings on the development of VAP. However, no relationship was found between the development of VAP and ventilator settings. The number of suctioning with open-suction systems was a risk factor for VAP, by frequently breaking the circuit. Avoidance of unnecessary suctioning and breaking of the circuit, overuse of sedatives and enteral nutrition will prevent the development of VAP.

Conflict of Interest

No conflict of interest was declared by the authors.

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